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Vinorelbine (Navelbine®). A New Semisynthetic Vinca Alkaloid

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Summary and Key Words

Vinorelbine (Navelbine®) is a new, semisynthetic 5'Nor-vinca-alkaloid, modified on the catharantine ring, developed by Pierre Fabre Médicament. Vinorelbine is as potent as the other vinca alkaloids to inhibit mitotic microtubule polymerization. On the other hand, its activity is lower on axonal microtubule. Preclinical studies have shown its broad spectrum of activity in vitro and its antitumoral efficacy comparable or higher to that of other vinca alkaloids against murine tumors and in xenograft models. The main experimental toxicity of vinorelbine is a reversible leucopenia. No neurotoxicity was evidenced in rats, dogs and monkeys.

After i.v. injection in patients, the plasma kinetic is described by a tricompartimental model with a high clearance, a very large volume of distribution and a long terminal half life, intermediate between vincristine and vinblastine. Tissue uptake of vinorelbine is very intense, probably related to its high liposolubility, leading to high tissue concentration compared to plasma.

Phase I trial using weekly i.v. administration demonstrated a maximal tolerated dose (MTD) of 27.5 to 35.4 mg/m^2 and the recommended dose was established at 30 mg/m^2 weekly. In Phase II studies, Vinorelbine was shown to be effective in at least 4 types of cancer: Non-small cell lung cancer (remission rate: 33%), breast cancer (45%), advanced ovarian cancer (15% in heavily pretreated patients), Hodgkin's disease (90%).

In all the trials, side effects are generally limited to a reversible and non-cumulative leucopenia. Neurotoxicity appears to be mild, similar to that observed with vinblastine and much less severe than with vincristine. No evidence of cardiac, pulmonary, renal, hepatic or other organ system toxicity has emerged.

Vinorelbine appears to be an original and promising anticancer agent which shows a large spectrum of antitumor activity and reduced side effects.

Vinorelbine · Vinca alkaloids · Preclinical studies · Phase-I/II trials

Zusammenfassung und Schlüsselwörter

Vinorelbin (Navelbine®)ist ein neues semisynthetisches 5'Nor-Vincaalkaloid, das am Catharantinring modifiziert ist. Es wurde von Pierre Fabre Médicament entwickelt. Es ist im Sinne der Hemmung der mitotischen Mikrotubulipolymerisation ebenso potent wie andere Vincaalkaloide. Auf der anderen Seite ist seine Aktivität auf die axionalen Mikrotubuli niedriger. Präklinische Studien haben sein breites Aktivitätsspektrum in vitro und seine antitumorale Wirksamkeit gezeigt, die im Vergleich zu anderen Vincaalkaloiden bei murinen Tumoren oder in Xenograft-Modellen ähnlich oder höher ist. Die wichtigste experimentelle Toxizität von Vinorelbin ist eine reversible Leukopenie. Bei Ratten, Hunden und Affen wurde keine Neurotoxizität nachgewiesen.

Nach i.v.-Injektion bei Patienten wurde eine Plasmakinetik im Sinne eines Dreikompartmentmodells mit hoher Clearance, einem sehr hohen Verteilungsvolumen und einer langen terminalen Halbwertszeit beschrieben, die zwischen Vincristin und Vinblastin liegt. Die Gewebsaufnahme von Vinorelbin ist sehr intensiv, wahrscheinlich wegen seiner hohen Fettlöslichkeit, was zu einer hohen Gewebskonzentration im Vergleich zum Plasma führt.

Klinische Phase-I-Studien mit wöchentlicher i.v.-Gabe zeigten eine maximal tolerable Dosis (MTD) von 27,5 bis 35,4 mg/m^2; die empfohlene Dosis liegt bei 30 mg/m^2 wöchentlich.

In Phase-II-Studien zeigt Vinorelbin eine Wirksamkeit wenigstens bei vier Tumoren: Nicht-kleinzelliges Bronchialkarzinom (Remissionsrate 33%), Mammakarzinom (45%), fortgeschrittenes Ovarialkarzinom (15%, bei stark vorbehandelten Patienten), Morbus Hodgkin (90%). Bei allen Studien waren die Nebenwirkungen auf eine reversible und nicht kumulative Leukopenie begrenzt. Die Neurotoxizität scheint mild zu sein, ähnlich wie bei Vinblastin und viel geringer als bei Vincristin. Eine kardiale, pulmonale, renale, hepatische oder andere Organtoxizität wurde nicht beobachtet.

Vinorelbin scheint eine vielversprechende antineoplastische Substanz zu sein, die ein breites Aktivitätsspektrum und reduzierte Toxizität zeigt.

Vinorelbine · Vincaalkaloide · Präklinische Prüfung · Phase-I/II-Prüfung

Introduction

The vinca alkaloids played a major role in cancer chemotherapy since the 1960's. Investigations of extracts from the periwinkle plant, Vinca Rosea, led to the isolation of vinblastine and vincristine. These alkaloids are dimeric structures composed of an indole nucleus (catharanthine) linked to a dihydroindole nucleus (vindoline). In 1975, the first semisynthetic vinca alkaloid, vindesine, was synthetized. The difference between these three vinca alkaloids only consists in the nature of the substituents on the vindoline ring.

An original chemical reaction developed by Potier [1] (Gif-sur-Yvette) led for the first time to a modified structure of the catharanthine nucleus. After condensation with vindoline, a family of new derivatives was obtained, among which vinorelbine was selected for its powerful inhibitory effect on tubulin polymerization and low spiralization activity. Further studies, preclinical and clinical, confirmed the particular antitumoral properties of the molecule.

Vinorelbine, developed by the French Company Pierre Fabre

[1] Pierre Fabre Médicament, Boulogne, France

Médicament, has obtained a marketing approval in France for the treatment of non-small cell lung cancer; other indications are currently under investigation. Results so far obtained in breast cancer appear especially promising.

Toxicology, Pharmacology and Pharmacokinetics

The dose limiting toxicity of vinorelbine is leucopenia. Transient increase in SGOT and SGPT were noted in rats and dogs but not in monkeys. Its neurological potential is very limited. Unlike vincristine, vinorelbine does not inhibit spermatogenesis and does not lead to important gastrointestinal effects. Vinorelbine inhibits microtubule assembly, thereby blocking formation of the mitotic spindle apparatus which is necessary for cell division.

In intact tectal plates from mouse embryos, vinorelbine, vincristine and vinblastine were equipotent to induce a depolymerization of mitotic microtubules, but vinorelbine was less active on axonal microtubules than the other vinca alkaloids [2]. The rate and extent of vinorelbine induced tubulin aggregation is much lower than those of vincristine and vinblastine. Moreover, vinorelbine is the only vinca alkaloid that discriminates between the various types of microtubules [3]. Since neurotoxicity may be mediated by spiralization of axonal microtubules, these data are consistent with an improved therapeutic index for vinorelbine. The drug is cytostatic at nanomolar concentrations, in vitro, against a variety of human tumor cell lines (leukemia, non-small cell and small cell lung cancer, colon and breast cancer, malignant melanoma and brain tumors).

Against murine tumors, L_{1210} leukemia, B_{16} melanoma and P_{388} leukemia, antitumoral activity of vinorelbine was equal and often higher compared to that of other analogues both in terms of survival time and long term survivors. Antitumoral activity was higher when the drug was administered by i.v. route.

Vinorelbine developed a high activity against human tumor xenografts on nude mice: LX_1, Q_{90}, LC_{06} (small cell lung carcinoma), L_{27}, QG_{56} (non-small cell lung carcinoma), MX_1 (mammary adenocarcinoma), ST_4 and ST_{40} (stomach tumors) [4]. In vivo, vinorelbine combination with etoposide or cisplatinum produces additive effects with a marked increase in survival time and long term survival without increased toxicity.

After i.v. injection, the plasma kinetics of vinorelbine are described by a bi or tricompartimental model, with a high clearance, a very large volume of distribution and a long terminal half life (40 h for human beings), intermediate between vincristine and vinblastine [5, 8, 9]. Vinorelbine is rapidly and avidly taken up and retained in a wide variety of tissues. Tissues to plasma ratio is large, ranging from 20.1 to 88.1 except in fat and brain [5]. When compared with vincristine and vindesine, tissue concentration is higher for vinorelbine in spleen, kidney, stomach and lung. Vinorelbine is predominantly excreted by fecal route via an intense biliary excretion [5–10]. The remainder (8 to 14%) is excreted in the urine. Overall recovery is incomplete as it was observed with other vinca alkaloids even after 3 or 4 weeks. Despite extensive work performed so far, the metabolic pattern of vinorelbine presently is not fully known. The only metabolite identified is desacetyl vinorelbine, a derivative presenting the same activity and toxicity than the parent compound [5, 6].

Clinical Studies

Phase I Studies

The first Phase I study [11] included 30 evaluable patients (median WHO performance status of 2) with a variety of hematological (n = 19) or solid (n = 11) tumors, all heavily pretreated with multiple polychemotherapies including sometimes three different vinca alkaloids. They were treated with vinorelbine on a weekly schedule, starting at a dose of 3 mg/m^2 up to 36 mg/m^2. Cohorts of at least two patients were treated according to a modified Fibbonacci schedule.

The dose limiting toxicity was hematologic, specifically leukopenia and neutropenia. At 27.5 mg/m^2/week, 54% of patients experienced Grade 3 or 4 neutropenia during 12% of cycles. At 35.4 mg/m^2/week, 20% of patients during 8% of dosing cycles experienced Grade 3 neutropenia. Platelets were relatively unaffected; only one of the 18 patients treated at the 27.5 mg/m^2 level exhibited a Grade 3 thrombocytopenia. Anemia, while frequent, was moderate even at the highest dose. White count nadirs for Grade 3 and 4 toxicity typically occurred at day 7 to 10 with full recovery in all cases at 1 to 3 weeks. Because of the relatively rapid onset and recovery of myelosuppression, a weekly dose schedule was feasible. Non-hematologic side-effects were mild. Neurotoxicity Grade 1 (consisting of paresthesia) was observed in two patients, one at 27.5 mg/m^2 and the other at 35.4 mg/m^2. In this study, 2 partial responses (1 in a patient with Hodgkin's disease and 1 in Non-Hodgkin's lymphoma) and 3 minor responses were obtained.

Phase II Studies

Phase II studies were performed in advanced non small cell lung cancer (NSCLC), breast cancer, ovarian cancer, Non-Hodgkin's and Hodgkin's lymphoma (Table 1).

NSCLC [13]: Because preclinical data suggested that vinorel-

Table 1. Antitumor efficacy of Vinorelbine (VIN) in phase II studies

Type of cancer	Treatment	Line	n	CR	PR	Objective Response rate (%)
NSCLC	VIN	1st	69		23	33
Ovarian cancer	VIN	2 +	32	1	4	15
Hodgkin's disease	VIN	1st	30**	1	26	90
Hodgkin's disease	VIN	2 +	17		6	
Non-Hodgkin's Lymphoma**	VIN	2 +	18	2	5	37
Breast cancer	VIN	1st	25	5	10	60
Breast cancer	VIN	1st	131	11	48	45
Breast cancer	VIN	2nd	33	2	7	24
Breast cancer	VIN + 5FU	1st	27	8	11	70
Breast cancer	VIN + Adriamycin	1st	38	9	21	79

*Clinical responses, **high grade and low grade.

bine concentrates in lung tissue and is active against NSCLC human tumor cell lines, the first Phase II study was conducted in 78 previously untreated patients with inoperable progressing NSCLC showing a sufficient performance status.

Most of the patients were elderly (median age 64) and male (n = 75). The histological examination led to the following classification: Squamous cell carcinoma (n = 57), adenocarcinoma (n = 15), undifferentiated (n = 6). Patient distribution according to stage was: Stage I–II 8, stage IIIA–IIIB 29 and stage IV 41. Patients were treated with i.v. vinorelbine on a weekly schedule at an average dose of 30 mg/m^2 (range 21.6–37.7), diluted in 125 ml of normal saline and infused over 20 min. Treatment was continued until progression or Grade 4 toxicity appeared. The median number of treatment cycles was 8 (range 1–59) days and the median interval between the cycles was 8 (range 5–57) days.

The 78 patients received 981 cycles at a mean dose of 29.3 mg/m^2. All patients were evaluable for tolerance and 69 for response. There were 23 partial responses yielding an objective response rate of 33.3% (confidence interval 22–44%). The median onset of response was eight cycles and the median duration of response 34 weeks. The median survival time was 32 weeks for all patients and 63 weeks for responders. Eight patients had durable response lasting more than one year.

The most frequent and clinically important toxicity was myelosuppression. Grade 3 and 4 granulocytopenia occurred in more than half of the patients, corresponding to 21% of evaluable cycles. Approximately one-third of the dosing cycles were delayed due to leucopenia. This toxicity is not cumulative and readily reversible upon discontinuation of the drug. Mild to moderate anemia was common; thrombocytopenia, however, did not occur.

Due to the known risk of neurotoxicity with the vinca alkaloids, all patients were carefully monitored for signs and symptoms of neurotoxicity (constipation, maxillary pain and peripheral neuropathies) in this Phase II trial. Mild to moderate constipation occurred in 33.8% of patients during 8.9% of the dosing cycles; 6 patients presented constipation Grade 3 or 4. Some evidence of peripheral neuropathy (primarily loss of deep tendon reflexes) was prevalent but generally mild. All patients treated for longer than six months (n = 8) experienced abolition of deep tendon reflexes, suggesting that this is a cumulative toxicity of vinorelbine. Grade 1 or 2 paresthesias were experienced by 5.2% of patients. Nine patients (11.5%) experienced Grade 3 toxicity (asthenia and decreased muscular force). Electrophysiologic studies were done at baseline and at the end of week eight (or a total dose of 240 mg/m^2) to determine qualitative and quantitative effects of vinorelbine administration on neurologic function. There were no effect on cutaneous sensory nerve fibers (Type II fibers) and motor nerve fibers. However, proprioceptive nerve fibers (Type I fibers) of the sural triceps showed evidence of moderate axonal degeneration.

Grade 3–4 local cutaneous reactions at the site of injection occurred in 10% of the patients corresponding to 1.7% of the cycles.

Gastrointestinal toxicity was unfrequent and generally mild: 80% of the patients did not suffer from nausea or vomiting. 75% of them did not experience any alopecia. Two patients (2.7%) presented allergic reactions and one patient experienced bronchospasm 30 min after receiving a 2nd course of vinorelbine, not repeated on rechallenge.

Advanced Ovarian Cancer [14]: 38 patients with advanced ovarian cancer were enrolled in a Phase II trial. All patients had at least one prior surgical procedure and at least one cisplatinum-containing regimen. 12 patients (32%) had failed to two prior regimens. 10 patients had received radiation: 3 on the pelvic area only and 7 on both the pelvis and abdomen. In the 32 evaluable patients, the objective response rate was 15% with one complete response lasting 73 weeks and four durable partial responses, lasting 10, 11, 17 and 47 weeks, respectively. Vinorelbine was generally well tolerated. The dose-limiting toxicity was myelosuppression; 38% of the patients experienced Grade 4 neutropenia corresponding to 9% of cycles. Grade 3–4 non-hematological toxicity included nausea-vomiting (8%), alopecia (8%), constipation (14%), peripheral neuropathy (5%) and local cutaneous reaction (5%).

Malignant Lymphoma: 32 patients, aged 5 to 60 years, with a bulky or extended non-pretreated Hodgkin's disease [15], were treated with vinorelbine 30 mg/m^2/week for four weeks prior to receiving standard therapy with MOPP-ABVD. In 27 of the 30 evaluable patients, a reduction of the initial tumor volume greater than 50% was observed after one or two vinorelbine injections. Vinorelbine was well tolerated over this short course of therapy, Grade 3 or Grade 4 neutropenia was seen in 2% and 1% of cycles, respectively. No nausea/vomiting or constipation was noted. One patient experienced a Grade 2 decrease of deep tendon reflexes and two patients mild to moderate transient paresthesias.

A further Phase II trial was instituted for patients with pretreated Hodgkin's disease and non-Hodgkin's lymphomas [16]. 53 patients entered this trial, all heavily pretreated with several chemotherapy regimens and, for most of them, by radiotherapy. Vinorelbine was administered at the same dose and schedule. Out of 17 evaluable patients with Hodgkin's disease, 6 partial remissions (8–30 weeks duration) and 8 minor responses or stabilisation were obtained. Among the 9 evaluable patients with non-Hodgkin's lymphoma, 2 complete remissions, 1 partial remission and 1 stabilisation were observed. Out of 9 patients with low grade non-Hodgkin's lymphoma, 4 achieved a partial remission and another 4 had stable disease. The overall response rate in this very heavily pretreated population is of interest (37%). The mean response duration is rather short (12 weeks), but could be explained by the fact that these patients had exhausted all the therapeutics possibilities.

Advanced Breast Cancer: 6 Phase II studies have now been completed: Two in first Line treatment and two in second and third line. In these 4 studies, vinorelbine was given as single agent. In the other 2 trials, vinorelbine was combined with either 5-fluorouracil or adriamycin in non pretreated patients. In the preliminary first Line vinorelbine Study [17] for 25 evaluable patients, a high response rate of 60% (5 complete and 10 partial remissions) was obtained, with a median response duration of 22 weeks. However, it has to be noticed that the patients included in this study are not representative since 65% of them presented only one metastatic site and lymph node metastases were the target site in 44%.

Therefore, the second first Line Study [18] included a large population (157 patients), stratified for metastatic targets.

36%, 39% and 25% of the patients, respectively presented 1, 2 or 3 and more metastatic sites. The overall response rate achieved was 45% (confidence interval: 36–53%), with 11 complete and 48 partial remissions for 145 evaluable patients. The rate of response according to metastatic site ranged between 24% (liver) and 67% (skin). The median duration of response was 32 weeks.

In second/third line treatment of metastatic breast cancer, the 2 studies [19, 20] involving 50 and 33 patients respectively pretreated by anthracyclines in more than 80% of cases, led to conclusive results. Response rates of 24% and 30% were obtained and the median response durations were 15 and 21 weeks. In both studies, the target sites were liver and lung metastases for half of the patients.

The high efficacy of vinorelbine as single agent was further increased by combination with 5-fluorouracil or adriamycin. Vinorelbine (30 mg/m^2, day 1 and 5), combined with 5-fluorouracil (750 mg/m^2, day 1–5) every 3 weeks, in 27 patients non previously treated for metastatic disease, led to a response rate of 70.3% (8 complete and 11 partial remissions). The median duration of response was 44 weeks. Similarly, high response rates of 79% (9 complete and 21 partial remissions out of 38 patients) was obtained when vinorelbine (25 mg/m^2, day 1 and 8) was combined with adriamycin (50 mg/m^2), every 3 weeks [22]. In this study, response duration is not yet evaluable, since 32 patients are still under evaluation.

In all these studies, granulocytopenia has been the dose limiting toxicity, with 50% or more patients presenting a Grade 3–4 toxicity. Although granulopenia is essentially not cumulative and, in most cases, rapidly reversible, and resulting in only few infections episodes (less than 15%), treatment had to be delayed in a significant number of courses, suggesting a dose intensity of approximatively 60%.

The three Phase II trials indicate a high efficacy of vinorelbine in advanced breast cancer as evaluated in non randomized studies. Its high response rates are very unusual for vinca alkaloids, and allow the postulation that this drug might be one of the most active agent in this indication.

Non Conclusive and Ongoing Studies

At the usual dose and schedule (30 mg/m^2/week), vinorelbine has not shown evidence of activity for advanced colorectal cancer for pretreated head and neck as well as renal cell carcinoma. Other types of cancer are presently under investigation such as small cell lung cancer, testicular cancer, malignant melanoma, kidney and cervix carcinoma. Moreover, another schedule of administration (4 days continuous infusion) is also under study. Finally, the oral route of administration appears to be particularly promising. Formulation problems, however, still have to be solved to increase the stability of the drug before resorption.

Conclusion

The experiences so far obtained with vinorelbine suggest that this drug may have significant advantage over the other chemi-

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cal vinca alkaloids. The favourable response rates and significant number of durable responses obtained in NSCLC appear to be particularly interesting.

The present data obtained by vinorelbine for treatment of advanced breast cancer indicate response rates higher than 40% in first Line, higher than 20% in second Line, within combination chemotherapy, using 5-Fluorouracil or Adriamycin about 70%. The rate of complete remissions in vinorelbine monotherapy ranges from 5–26%, the response duration from 16–44 weeks.

The activity of vinorelbine for malignant lymphoma appears to be very promising, although not yet completely documented. The activity in ovarian cancer deserves further investigation. The very limited peripheral neurotoxicity induced by vinorelbine is unusual for vinca alkaloids. It might be explained by the more specific effect of the compound in mitotic microtubules, as well as its reduced spiralizating effect.

References

1 Potier P: The synthesis of Navelbine, prototype of a new series of vinblastine derivatives. Sem Oncol 1989;16(Suppl 4):2–4.

2 Binet S, Fellous A, Meininger V: In situ analysis of the action of Navelbine® on various types of microtubules using immunofluorescence. Sem Oncol 1989;16(Suppl 4):5–8.

3 Fellous A, Ohayon R, Vacassin T, et al: Biochemical effects of Navelbine on tubulin and associated proteins. Sem Oncol 1989;16(Suppl 4):9–14.

4 Cros S, Wright M, Morimoto M, et al: Experimental antitumor activity of Navelbine. Sem Oncol 1989;16(Suppl 4):15–20.

5 Krikorian A, Rahmani R, Bromet N, et al: Pharmacokinetics and metabolism of Navelbine. Sem Oncol 1989;16(Suppl 4):21–25.

6 Rahmani R, Bore P, Favre R, et al: Preliminary studies on Vindesine (VDS) and Navelbine (NVB) metabolism using both human isolated hepatocytes and microsomal fractions. Proc. 5th NCI/EORTC symposium on new drugs in cancer therapy. Amsterdam, Oct. 22–24, 1986, Abstr 10 and 12.

7 Bromet N, Krikorian A, Bernouillet C: Study of the tissues distribution of H3-Navelbine after single oral and i.v. administration of H3-NVB ditartrate in monkey. 2nd international ISSX meeting, Kobe, Japan, May 16–20, 1988.

8 Rahmani R, Martin M, Barbet J, et al: Radioimmunoassay and preliminary pharmacokinetic studies in rats of 5-Noranhydrovinblastine (Navelbine). Cancer Research 1984;44:5609–5613.

9 Bore P, Rahmani R, Van Cantfort J, et al: Pharmacokinetics of a new anti-cancer drug, Navelbine, in patients. Cancer Chemother Pharmacol 1989;23:247–251.

10 Rahmani R, Bruno R, Iliadis A, et al: Clinical pharmacokinetics of the antitumor drug Navelbine. Cancer Research, 1987;47:5796–5799.

11 Mathe G, Reizenstein P: Phase I pharmacologic study of a new vinca alkaloid: Navelbine. Cancer Letters 1985;27:285–293.

12 Favre R, Garnier G, Depierre A, et al: A Phase I study of Navelbine (Nor-5'-Anhydrovinblastine). Recent advances in chemotherapy. Joji Ishigami, University of Tokyo Press, 1985.

13 Depierre A, Lemarié E, Dabouis G, et al: Efficacy of Navelbine (NVB) in non-small cell lung cancer. Sem Oncol 1989;16(Suppl 4):26–29.

14 George MJ, Heron JF, Kerbrat P, et al: Navelbine in advanced ovarian epithelial cancer: A study of the French oncology centers. Sem Oncol 1989;16(Suppl 4):30–32.

15 Benchemsi N, Chouffai Z, Benchekroun S, et al: Clinical evaluation of Navelbine® (NVB) efficacy in non pretreated advanced Hodgkin disease (HD). Europ Soc Med Oncol 1988;29(P):C8.

16 Eghbali H: Phase II study of Vinorelbine (Navelbine®) in previously treated Hodgkin's disease and non Hodgkin's lymphoma. Navelbine actuality and perspectives. Montrouge, Libbey, 1991 (in preparation).

17 Canobbio L, Pastorino G, Brema F, et al: Efficacy of Navelbine® in advanced breast cancer. Sem Oncol 1989;16(Suppl 4):33–36.

18 Fumoleau P, Delgado FM, Delozier T: Phase II trial with Navelbine (NVB) in advanced breast cancer. Am Soc Clin Oncol 1990;21:76.

19 Fumoleau P, Roche H, Pinon G, et al: Navelbine as second line chemotherapy in metastatic breast carcinoma (MBC); An ARTAC Phase II trial. Proc Am Ass Cancer Res 1990;207:1232.

20 Dieras V, De Cremoux P, Extra JM, et al: A two stage sequential phase II study of vinorelbine in patients with previously treated advanced breast cancer. Breast Cancer Res Treat 1989;14:146 (53).

21 Dieras V, Extra JM, Morvan F, et al: Phase II study of Navelbine (NVB) and Fluoro-uracil (FU) in patients with metastatic breast cancer (MBC) using a group sequential design. Europ Soc Med Oncol 1990 (in preparation).

22 Spielmann M, Jouve M, Turpin F, et al: Pilot phase II study with Navelbine (NVB) – Adriamycine (ADR) Combination in advanced breast cancer (ABC). 13th San Antonio Breast Cancer Symposium 1989 (in preparation).

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